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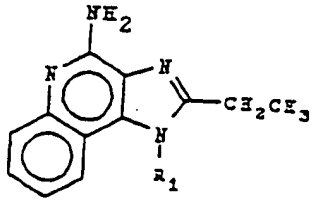

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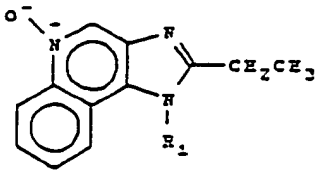

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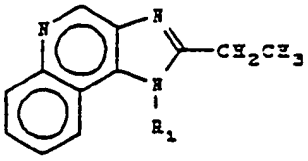

( III )

(57) Abstract

2-Ethyl 1H-imidazo[4,5-c]quinolin-4-amines f formula (I), active as immunomodulators and antiviral agents. Also, intermediates of formulae (II, III) in the preparation of such compounds, pharmaceutical compositions, and pharmacological methods of use.

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# ANTIVIRAL 2-ETHYL-1H-IMIDAZO(4,5-C)QUINOLIN-4-AMINES

## BACKGROUND OF THE INVENTION

### Field of the Invention

This invention relates to 1H-imidazo[4,5-c]-quinoline compounds. In other aspects, this invention relates to 1H-imidazo[4,5-c]quinolin-4-amines, intermediates for the preparation of such compounds, pharmaceutical compositions containing such compounds, and pharmacological methods of using such compounds. This invention also relates to methods of inducing biosynthesis of tumor necrosis factor.

### Description of the Related Art

The first reliable report of the 1H-imidazo-[4,5-c]quinoline ring system, Backman et al., J. Org. Chem. 15, 1278-1284 (1950), describes the synthesis of 1-(6-methoxy-8-quinolinyl)-2-methyl-1H-imidazo[4,5-c]-quinoline for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1H-imidazo[4,5-c]quinolines have been reported. For example, Jain et al., J. Med. Chem. 11, pp. 87-92 (1968), has synthesized the compound 1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline as a possible anticonvulsant and cardiovascular agent. Also, Baranov et al., Chem. Abs. 85, 94362 (1976), has reported several 2-oxoimidazo[4,5-c]quinolines, and Berenyi et al., J. Heterocyclic Chem. 18, 1537-1540 (1981), has reported certain 2-oxoimidazo[4,5-c]-quinolines.

Certain antiviral 1H-imidazo[4,5-c]quinolin-4-amines are described in U.S. Pat. No. 4,689,338 (Gerster). These compounds are substituted on the 1-position by alkyl, hydroxyalkyl, acyloxyalkyl, benzyl, phenylethyl or substituted phenylethyl, and at the 2-position with hydrogen, alkyl, benzyl, or

substituted benzyl, phenylethyl or phenyl. Furthermore, these compounds ar known to induce interferon biosynthesis. Other antiviral 1H-imidazo[4,5-c]quinolin-4-amines, substituted on the 1-position by alkenyl substituents, are described in U.S. Pat. No. 4,929,624 (Gerster).

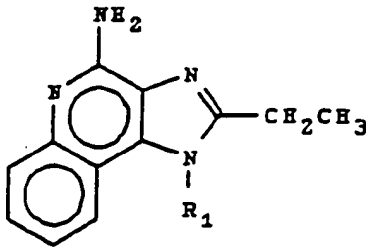
U.S. Pat. No. 4,698,348 (Gerster) discloses 1H-imidazo[4,5-c]quinolines that are active as bronchodilators, such as 4-substituted 1H-imidazo-[4,5-c]quinolines wherein the 4-substituent is, inter alia, hydrogen, chloro, alkylamino, or dialkylamino, and the 2-substituent is, inter alia, hydroxyalkyl, aminoalkyl, or alkanamidoalkyl. Said patent also discloses 3-amino and 3-nitro quinoline intermediates substituted at the 4-position by hydroxyalkylamino or cyclohexylmethylamino, and 1H-imidazo[4,5-c]quinoline N-oxide intermediates substituted at the 2-position with, inter alia, hydroxyalkyl, aminoalkyl, or alkanamidoalkyl.

Tumor necrosis factor (TNF) is an endogenic glycoprotein that has the capability to selectively destroy tumor cells. For this reason there is considerable interest in TNF as a cancer therapeutic agent.

Biosynthesis of tumor necrosis factor has been induced by immunomodulators such as interleukin-2, and by catabolic enzymes such as those disclosed in European Patent Application 0,421,023A (Ransberger et al.).

## DETAILED DESCRIPTION OF THE INVENTION

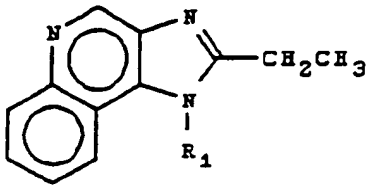
This invention provides compounds of Formula I:



I

wherein $R_1$ is 2-methylpropyl or 2-hydroxy-2-methylpropyl.

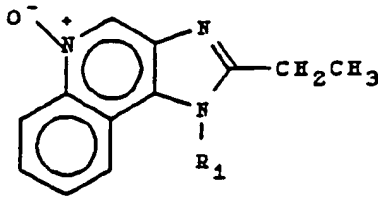
This invention also provides intermediate compounds of Formula II:



II

wherein $R_1$ is defined above.

This invention also provides intermediate compounds of Formula III:



III

wherein $R_1$ is as defined above.

The compounds of the invention can be prepared as set forth in the Examples below.

A compound of Formula I can be used in the form of a free base or it can be used in the form of a pharmaceutically acceptable acid-addition salt such as a hydr chl ride, dihydrogen sulfate, trihydrogen

phosphate, hydrogen nitrate, methanesulfonate or a salt of another pharmaceutically acceptable acid. A pharmaceutically acceptable acid-addition salt of a compound of Formula I can be prepared by reaction of the compound with an equimolar amount of a relatively strong acid, preferably an inorganic acid such as hydrochloric, sulfuric, or phosphoric acid, or an organic acid such as methanesulfonic acid, in a polar solvent. Isolation of the salt is facilitated by the addition of a solvent, such as diethyl ether, in which the salt is insoluble.

The compounds of Formula I can be utilized to achieve a desired pharmacological effect by administration to a patient in an appropriately formulated pharmaceutical composition. Suitable pharmaceutical compositions comprise a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula I. The amount or concentration of a compound of Formula I that constitutes a therapeutically effective amount will depend of course on the particular desired pharmacological effect, on the route of administration, and on the particular formulation being used. Suitable therapeutically effective amounts can be selected by those skilled in the art.

Suitable pharmaceutical compositions include those suitable for oral, parenteral (including subcutaneous, intramuscular, intraperitoneal, and intravenous), buccal, rectal, or transdermal administration, or administration by inhalation.

Pharmaceutical compositions for oral administration can take the form of tablets, capsules, suspensions, solutions, or emulsions. Tablets can comprise pharmaceutically acceptable excipients such as diluents, binding agents, lubricants, disintegrants, flavors, colors, and the like. Liquid preparations can be prepared by conventional means with pharmaceutically

acceptable excipients such as suspending agents, emulsifying agents, vehicles, preservatives, colors, sweetening agents, and the like. Compositions for oral administration can be formulated to give controlled release of the active compound by use of suitable pharmaceutically acceptable polymers.

Pharmaceutical compositions for parenteral administration can take the form of solutions, suspensions, or emulsions in aqueous or oily vehicles and can comprise pharmaceutically acceptable excipients such as buffering agents, tonicity adjusters, suspending agents, emulsifiers, and the like.

Pharmaceutical compositions for buccal administration can take the form of tablets or lozenges. Alternatively, the active compound can be incorporated into a transmucosal delivery device. Transmucosal delivery devices can comprise a backing and a matrix containing the active compound, a buccal adhesive, and optionally a penetration enhancer.

Pharmaceutical compositions for rectal administration can take the form of suppositories prepared by combining the active compound with conventional suppository bases.

Pharmaceutical compositions for transdermal administration can take the form of creams or lotions comprising pharmaceutically acceptable excipients such as ointment bases, oils, preservatives, emulsifiers, skin penetration enhancers, and the like. Alternatively, the active compound can be incorporated into a transdermal delivery device. The transdermal delivery device can be in the form of a bandage comprising a backing layer, a reservoir containing the active compound, optionally with other excipients, optionally a rate controlling membrane, and means for securing the device to the skin. Alternatively, the transdermal delivery device can comprise a backing

layer with an adhesive matrix containing the active compound and optionally one or more excipients.

Pharmaceutical compositions for administration by inhalation can take the form of solutions, suspensions, or powders that can be delivered by means of a pressurized aerosol container or a nebulizer.

The compounds of Formula I exhibit antiviral activity in mammals. They can therefore be used to control viral infections. For example, a compound of Formula I can be used as an agent to control infections in mammals caused by Type II Herpes simplex virus. Compounds of Formula I can also be used to treat a herpes infection by oral, topical, or intraperitoneal administration.

The compounds of Formula I were tested and found to induce biosynthesis of interferon in human cells. The test methods and results are set forth below. These results suggest that compounds of the invention might be useful in treating other diseases such as rheumatoid arthritis, warts, eczema, Hepatitis B, psoriasis, multiple sclerosis, essential thrombocythaemia, cancer such as basal cell carcinoma, and other neoplastic diseases.

The compounds of Formula I have been shown by the test methods set forth below to induce biosynthesis of tumor necrosis factor (TNF) in human cells. Moreover, the compounds of Formula I induce TNF biosynthesis when administered at lower dose concentrations than structurally related compounds of the prior art. Thus the compounds of Formula I have potential as cancer therapeutic agents, e.g., for local (e.g., topical, rectal, vaginal) administration or aerosol administration.

In the following Examples, the particular materials and amounts thereof recited as well as ther conditions and details, should not be construed to unduly limit the invention.

EXAMPLE 1

2-Ethyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]quinoline

A 16.55 g (0.077 mol) portion of $N^4$-(2-methylpropyl)-3,4-quinolinediamine (U.S. Pat. No. 4,689,338 example 16) was suspended in 100 mL of propionic acid and then heated at 120°C for about 20 hours. After cooling to room temperature, the reaction mixture was poured into 300 mL of water, made basic with concentrated ammonium hydroxide, cooled in an ice bath and then extracted with diethyl ether. The volume of the ether extract was reduced under vacuum. The resulting precipitate was collected, rinsed with ether and dried to provide 11 g of crystalline solid, m.p. 72-73.5°C. Analysis: Calculated for $C_{16}H_{19}N_3$: %C, 75.8; %H, 7.6; %N, 16.6; Found: %C, 75.6; %H, 7.7; %N, 16.5.

EXAMPLE 2

2-Ethyl-1-(2-methylpropyl)-1H-imidazo-[4,5-c]quinoline 5N Oxide

A 9.92 mL portion of peracetic acid was added to a solution of 10.65 g (0.042 mol) of 2-ethyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]quinoline in 100 mL of ethyl acetate. The mixture was heated at reflux for about 2 hours and then cooled to room temperature. A precipitate was collected, rinsed with ethyl acetate and dried to provide 4 g of a yellow solid, m.p. 177-180°C. This material was used without further purification.

EXAMPLE 3

2-Ethyl-1-(2-methylpropyl)-1H-imidazo-[4,5-c]quinolin-4-amine

A 3.7 g (0.014 mol) portion of 2-ethyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]quinoline 5N oxide was suspended in 35 mL of methylene chloride, cooled in an ice bath and th n combined with 45 mL of chilled

ammonium hydroxide. The resulting two phase mixture was stirred vigorously with cooling in an ice bath while a solution of 2.87 g (0.015 mol) f tosyl chl ride in 30 mL of methylene chloride was slowly added. The reaction mixture was allowed to slowly warm to room temperature with stirring. The methylene chloride was evaporated to provide an orange solid which was collected, rinsed with water and air dried. The solid was then recrystallized from methylene chloride containing a trace of methanol to provide 2.7 g of a white solid, m.p. 233-234°C. Analysis: Calculated for $C_{16}H_{20}N_4$: %C, 71.6; %H, 7.5; %N, 20.9; Found: %C, 71.3; %H, 7.3; %N, 20.6.

EXAMPLE 4

α,α-Dimethyl-2-ethyl-1H-imidazo-[4,5-c]quinoline-1-ethanol

A mixture containing 15.4 g (0.067 mol) of 1-[(3-amino-4-quinolinyl)amino]-2-methyl-2-propanol (U.S. Pat. No. 4,689,338 example 189) and 14.5 mL (0.07 mol) of triethyl orthopropionate was heated at about 165°C for about 2 hours. The resulting solid was slurried in a mixture of ethyl acetate and ether, collected and dried to provide 15.2 g of a solid. This material was used without further purification.

EXAMPLE 5

2-Ethyl-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinoline 5N Oxide

Using the general method of Example 2, 15.2 g of α,α-dimethyl-2-ethyl-1H-imidazo[4,5-c]quinoline-1-ethanol was oxidized to provide 15.2 g of crude N oxide. A sample was dissolved in water then precipitated by the addition of sodium hydroxide. The precipitate was collected and dried to provide a solid, m.p. 245-250°C. Analysis: Calculated for $C_{16}H_{19}N_3O_2 + \frac{1}{2}H_2O$:

%C, 65.3; %H, 6.8; %N, 14.3; Found: %C, 65.2; %H, 6.4; %N, 14.0.

EXAMPLE 6

4-Amino-α,α-dimethyl-2-ethyl-1H-imidazo[4,5-c]-quinoline-1-ethanol

Using the general method of Example 3, 14.3 g (0.05 mol) of 2-ethyl-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinoline 5N oxide was aminated to provide 8.2 g of crude product. This material was recrystallized from 60 mL of ethanol to provide 6.4 g of solid, m.p. 222-225°C. Analysis: Calculated for $C_{16}H_{20}N_4O$: %C, 67.6; %H, 7.1; %N, 19.7; Found: %C, 67.6; %H, 7.1; %N, 19.7.

COMPARATIVE EXAMPLE C1

4-Amino-α,α,2-trimethyl-1H-imidazo[4,5-c]-quinoline-1-ethanol

A mixture containing 1.5 g (0.0056 mol) of 1-[(3-amino-2-chloro-4-quinolinyl)amino]-2-methyl-2-propanol (U.S. Pat. No. 4,988,815 example 13), 1.4 g (0.0085 mol) of triethyl orthoacetate and 4 mL of xylenes was heated at 135-140°C for 6 hours. The solution was evaporated to provide a beige oil comprising 4-chloro-α,α,2-trimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol which was used without further purification.

The crude material was combined with 15 mL of 15% methanolic ammonia and heated in a steel bomb at about 150°C for 7 hours. The reaction mixture was partially evaporated then diluted with a small amount of water. The resulting precipitate was collected, rinsed sequentially with methanol, water, then methanol and dried to provide 900 mg of crude product. The crude product was recrystallized from methanol/methylene chl ride to provide 500 mg of col rless crystals, m.p.

290-293°C. Analysis: Calculated for $C_{15}H_{18}N_4O$: %C, 66.6; %H, 6.7; %N, 20.7; Found: %C, 66.6; %H, 6.7; %N, 20.6.

COMPARATIVE EXAMPLE C2

2-Methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c]-quinolin-4-amine

This compound can be prepared by known methods. See for example U.S. Pat. No. 4,689,338 example 113.

COMPARATIVE EXAMPLE C3

1-(2-Methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine

This compound can be prepared by known methods. See for example U.S. Pat. No. 4,689,338 example 99 or U.S. Pat. No. 4,988,815 example 10.

COMPARATIVE EXAMPLE C4

4-Amino-α,α-dimethyl-1H-imidazo-[4,5-c]quinoline-1-ethanol

This compound can be prepared by known methods. See for example U.S. Pat. No. 4,689,338 example 189.

The 2-ethyl 1H-imidazo[4,5-c]quinolin-4-amines of the invention and comparative compounds were tested according to the methods set forth below:

TUMOR NECROSIS FACTOR (α) INDUCTION IN HUMAN CELLS

This test method is an assay for tumor necrosis factor (α) induction in human mononuclear cells in culture. Activity is based on the measurement of human tumor necrosis factor (α) secreted into culture medium. Human tumor necrosis factor (α) is measured by radioimmunoassay.

Blood Cell Preparation for Culture

Whole blood is collected by venipuncture into EDTA ($K_3$) vacutainer tubes. Peripheral bl d mononuclear

cells (PBM's) are prepared by LeucoPREP™ Brand Cell Separation Tubes (available from Becton Dickinson Labware, Lincoln Park, NJ) and cultured in RPMI 1640 medium (available from GIBCO, Grand Island, NY) supplemented with 25 mM HEPES (N-2-hydroxyethyl-piperazine-N'-2-ethanesulfonic acid) and L-glutamine with 1% penicillin-streptomycin solution added) with 10% autologous serum (heat inactivated, 56°C for 30 minutes) added. 200 μL portions of PBM's in medium are added to 96 well (flat bottom) MicroTest™ III tissue culture plates (available from Falcon Plastics, Oxnard, CA).

Compound Preparation

Test compounds are solubilized in water, ethanol or dimethyl sulfoxide then diluted with distilled water, 0.01N sodium hydroxide or 0.01N hydrochloric acid (The choice of solvent will depend on the chemical characteristics of the compound being tested.). It is preferred that the final concentration of ethanol or dimethylsulfoxide, if used, does not exceed 1%. Compounds are initially tested in a concentration range of about 0.5 μg/mL to about 5 μg/mL. Compounds which show induction at a concentration of 0.5 μg/mL are then tested in a concentration range of 0.01 μg/mL to 0.5 μg/mL/.

Incubation

The solution of test compound is added in a predetermined volume (less than or equal to 50 μL) to the wells containing 200 μL of PBM's in medium. Solvent and/or medium is added to control wells (i.e., wells containing no test compound) and as needed to the test wells in order to adjust the final volume of each well to 250 μL. The plates are covered with plastic

lids, vortexed gently and then incubated f r 18 hours at 37°C with a 5% carbon dioxide atmosphere.

Separation

Following incubation, the plates are covered with PARAFILM™ laboratory film and then centrifuged at 1000 rpm for 15 minutes at 4°C in a Damon IEC Model CRU-5000 centrifuge. Medium (about 200 μL) is removed from 4 to 8 wells and pooled into 2 mL sterile freezing vials. Samples are maintained at -70°C until analysis.

Tumor necrosis factor (α) analysis/calculation

Tumor necrosis factor (α) is measured using an Enzyme Immuno Assay (available from Biosource International, California). Results are expressed as picograms/mL based on a standard curve conducted for each assay. Lipopolysaccharide, a known inducer of tumor necrosis factor (α), is included in each assay and is used to provide a comparison of response for each culture and assay. Lipopolysaccharide has been evaluated in this test method over a range 0.01 to 5 μg/mL and typically gives a response of 1000 to 3000 picograms/mL.

RESULTS

The compounds of the invention and comparative compounds were screened side-by-side in two separate assays. The results are shown in Tables 1 and 2. The blood used to run the assay of Table 1 was obtained from a different donor than that used to run the assay of Table 2.

TABLE 1

TUMOR NECROSIS FACTOR (α) INDUCTION IN HUMAN CELLS

| Compound of Example | TNF (α) (picograms/mL) Dose Concentration (μg/mL) 0.5 | 1.0 | 5.0 | Solvent |
|---|---|---|---|---|
| 3 | 1109 | 1519 | 1274 | DMSO |
| 6 | 950 | 1938 | 3740 | DMSO |
| C1 | 438 | 653 | 2186 | DMSO |
| C2 | 617 | 849 | 1203 | DMSO |
| C3 | 235 | 302 | 380 | water |
| C4 | 671 | 295 | 607 | water |
| LPS | 2580 | 2681 | 2648 | water |
| Control | 90 | | | |

TABLE 2

TUMOR NECROSIS FACTOR (α) INDUCTION IN HUMAN CELLS

| Compound of Example | TNF (α) (picograms/mL) Dose concentration (μg/mL) 0.01 | 0.05 | 0.1 | 0.5 | Solvent |
|---|---|---|---|---|---|
| 3 | 19 | 126 | 408 | 1742 | DMSO |
| 6 | 26 | 94 | 262 | 1554 | DMSO |
| C1 | 17 | 48 | 43 | 613 | DMSO |
| C2 | 35 | 44 | 46 | 1076 | DMSO |
| C3 | 15 | 51 | 39 | 53 | water |
| C4 | 25 | 32 | 37 | 39 | water |
| LPS | 1620 | 1840 | 1812 | 1799 | water |
| Control | 42 | | | | |

The results in TABLES 1 and 2 show that the compounds of Examples 3 and 6 induce biosynthesis of TNF in human cells when administered at lower dose concentrations than structurally related compounds of the prior art.

INTERFERON (α) INDUCTION IN HUMAN CELLS

An in vitro human blood cell system was used to assess int rferon induction by compounds of the invention. Activity is based on the measurement of interferon secreted into culture medium. Interferon is measured by bioassay.

Blood Cell Preparation for Culture

Whole blood is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBM's) are prepared by LeucoPREP™ Brand Cell Separation Tubes (available from Becton Dickinson) and cultured in RPMI 1640 medium (available from GIBCO, Grand Island, NY) supplemented with 25 mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid) and L-glutamine (1% penicillin-streptomycin solution added) with 10% autologous serum (heat inactivated, 56°C for 30 minutes) added. 200 μL portions of PBM's in medium are added to 96 well (flat bottom) MicroTest™ III tissue culture plates (available Falcon Plastics).

Compound Preparation

The compounds are solubilized in water, ethanol or dimethyl sulfoxide then diluted with distilled water, 0.01N sodium hydroxide or 0.01N hydrochloric acid (The choice of solvent will depend on the chemical characteristics of the compound being tested.). Compounds are initially tested in a concentration range of from about 0.1 μg/mL to about 5 μg/mL. Compounds which show induction at a concentration of 0.5 μg/mL are then tested in a concentration range of 0.01 μg/mL to 5.0 μg/mL/.

Incubation

The solution of test compound is added in a volume (less than or equal to 50 μL) to the wells containing

200 μL of PBM's in medium. Solvent and/or medium is added to control wells (i.e., wells containing no test compound) and as needed to the test wells in order to adjust the final volume of each well to 250 μL. The plates are covered with plastic lids, vortexed gently and then incubated for 24 hours at 37°C with a 5% carbon dioxide atmosphere.

Separation

Following incubation, the plates are covered with PARAFILM™ laboratory film and then centrifuged at 1000 rpm for 15 minutes at 4°C in a Damon IEC Model CRU-5000 centrifuge. Medium (about 175 μL) is removed from 4 to 8 wells and pooled into 2 mL sterile freezing vials. Samples are maintained at -70°C until analysis.

Interferon Analysis/Calculation

Interferon is determined by bioassay using A549 human lung carcinoma cells challenged with encephalomyocarditis. The details of the bioassay method have been described by G. L. Brennan and L. H. Kronenberg in "Automated Bioassay of Interferons in Micro-test Plates", Biotechniques, June/July; 78, 1983. Briefly stated the method is as follows: interferon dilutions and A549 cells are incubated at 37°C for 12 to 24 hours. The incubated cells are infected with an inoculum of encephalomyocarditis virus. The infected cells are incubated for an additional period at 37°C before quantifying for viral cytopathic effect. The viral cytopathic effect is quantified by staining followed by spectrophotometric absorbance measurements. Results are expressed as (α) reference units/mL based on the value obtained for NIH HU IF-L standard. The interferon was identified as essentially all interferon (α) by testing in checkerboard neutralization assays against rabbit anti-human interferon (β) and goat anti-

human interferon (α) using A549 cell monolayers challenged with encephalomyocarditis virus.

RESULTS

Results are shown in Table 3 wherein the absence of an entry indicates that the compound was not tested at the particular dose concentration. Results designated as "<" a certain number indicate that interferon was not detectable in amounts above the lower sensitivity level of the assay.

TABLE 3

INTERFERON (α) INDUCTION IN HUMAN CELLS

| Compound of | Reference units/mL | | | | | |
|---|---|---|---|---|---|---|
| | Dose concentration (μg/mL) | | | | | |
| Example | 0.01 | 0.05 | 0.1 | 0.5 | 1.0 | 5.0 |
| 3 | 37 | 1200 | 190 | 1100 | 1000 | 640 |
| 6 | 4.3 | 67 | 110 | 150 | 150 | 110 |
| C1 | 4.2* | 406* | 619* | 493* | 557* | 557* |
| C2 | <1.8 | 140 | 250 | 750 | 750 | 750 |
| C3 | | | 10.5* | 340* | 550* | 296* |
| C4 | | | <6.4 | <6.4 | 1200 | 1200 |

*Average of the values obtained in three separate assays.

The results shown in TABLE 3 show that the compounds of Examples 3 and 6 induce biosynthesis of interferon in human cells.

ANTIVIRAL ACTIVITY IN GUINEA PIGS

The test methods described below demonstrate the ability of compounds of the invention to reduce the number and severity of lesions developed by guinea pigs infected with Type II Herpes simplex virus.

F male Hartley guinea pigs weighing 200 to 250 g are anesthetized with methoxyflurane (available under the tradename Metafane from Pitman-Moore, Inc., Washington Crossing, NJ), after which the vaginal area is swabbed with a dry cotton swab. The guinea pigs are then infected intravaginally with a cotton swab saturated with Herpes simplex virus Type II strain 333 ($1 \times 10^5$ plaque forming units/mL). Guinea pigs are assigned to groups of 7 animals; one group for each treatment and one to serve as a control (vehicle treated). The compounds of the invention are formulated in water containing 5% Tween 80 (a polyoxyethylene sorbitan monooleate available from Aldrich Chemical Company, Inc., Milwaukee, WI). The guinea pigs are treated orally once daily for four consecutive days starting 24 hours after infection.

Antiviral activity is evaluated by comparing lesion development in compound treated versus vehicle treated guinea pigs. External lesions are scored 4, 7, 8 and 9 days after infection using the following scale: 0 - no lesion, 1 - redness and swelling, 2 - a few small vesicles, 3 - several large vesicles, 4 - large ulcers with necrosis and 5 - paralysis. The maximum lesion score of each guinea pig is used to calculate the percentage lesion inhibition. The percentage lesion inhibition is calculated as follows:

$$100 - \frac{\text{Sum of maximum lesions scores of treat group}}{\text{Sum of maximum lesion scores of vehicle group}} \times 100$$

Results are shown in Table 4.

TABLE 4

ANTIVIRAL ACTIVITY IN GUINEA PIGS

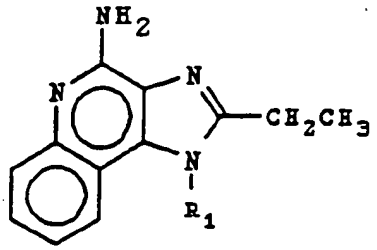
| Compound of Example | Dose mg/Kg | % Lesi n Inhibition |
|---|---|---|
| 3 | 0.3 | 56 |
| 3 | 0.1 | 13 |
| 3 | 0.03 | 37 |
| 6 | 1 | 100 |
| 6 | 0.5 | 100 |
| 6 | 0.3 | 93 |
| 6 | 0.1 | 0 |
| C1 | 0.5 | 100 |
| C1 | 0.1 | 50 |
| C2 | 2 | 100 |
| C3 | 3 | 96 |
| C3 | 2 | 56* |
| C3 | 1 | 14 |
| C4 | 1 | 100 |

*Average value from three separate assays

The results in TABLE 4 show that the compounds of Examples 3 and 6 reduce the number of lesions developed by guinea pigs infected with Type II Herpes simplex virus.

CLAIMS:

1. A compound of the formula:



wherein $R_1$ is 2-methylpropyl or 2-hydroxy-2-methylpropyl, or a pharmaceutically acceptable acid addition salt thereof.

2. An antiviral pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable vehicle, the compound being present in an amount effective to inhibit and/or prevent the progress of a viral infection.

3. A method of treating a mammal infected with a virus, comprising administering to the mammal a compound according to Claim 1 in an amount effective to inhibit and/or prevent the infection.

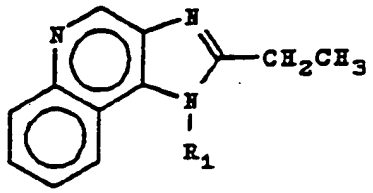
4. A method according to Claim 3, wherein the virus is Type II Herpes simplex.

5. A method of inducing interferon biosynthesis in a mammal, which method comprises administering to the mammal a compound according to Claim 1 in an amount sufficient to induce interferon biosynthesis.

6. A method of inducing tumor necrosis factor biosynth sis in a mammal, which method comprises administering to the mammal a compound according to

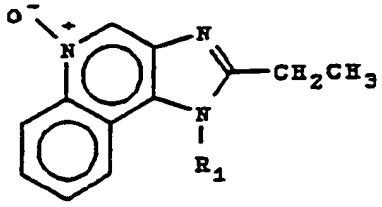
Claim 1 in an amount sufficient t induce tumor necr sis factor biosynthesis.

7. A compound of the formula:



wherein $R_1$ is 2-methylpropyl or 2-hydroxy-2-methylpropyl.

8. A compound of the formula:



wherein $R_1$ is 2-methylpropyl or 2-hydroxy-2-methylpropyl.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/09018

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D471/04; A61K31/44; //(C07D471/04,235:00,221:00)

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl. 5 | C07D ; A61K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category[10] | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| X | EP,A,0 145 340 (RIKER LABORATORIES) 19 June 1985 cited in the application see claims 1,2,9,12 | 1,2,7,8 |
| X | EP,A,0 385 630 (RIKER LABORATORIES) 5 September 1990 see claims 5,7 | 1,7 |
| A | EP,A,0 389 302 (RIKER LABORATORIES) 26 September 1990 cited in the application see claims 1,4 | 1,2 |

* Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 25 JANUARY 1993 | 01.03.93 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUR PEAN PATENT FFICE | VOYIAZOGLOU D. |

Form PCT/ISA/210 (second sheet) (January 1985)

# . INTERNATIONAL SEARCH REPORT

I. national application No.

PCT/US 92/ 09018

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

"Remark: Although claims 3 - 6 are directed to a method of treatment of (diagnostic method practised on ) the human/animal body the search has been carried out and based on the alleged effects of the compound/ composition."

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9209018 SA 66075

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent ffice EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 25/01/93

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| EP-A-0145340 | 19-06-85 | AU-A- | 2991189 | 15-06-89 |
| | | AU-B- | 581190 | 16-02-89 |
| | | AU-A- | 3540284 | 23-05-85 |
| | | CA-A- | 1271477 | 10-07-90 |
| | | EP-A,B | 0310950 | 12-04-89 |
| | | JP-A- | 60123488 | 02-07-85 |
| | | US-A- | 4698348 | 06-10-87 |
| | | US-A- | 4689338 | 25-08-87 |
| EP-A-0385630 | 05-09-90 | AU-B- | 630921 | 12-11-92 |
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| | | JP-A- | 3027380 | 05-02-91 |
| EP-A-0389302 | 26-09-90 | US-A- | 4929624 | 29-05-90 |
| | | AU-A- | 5142690 | 27-09-90 |
| | | CA-A- | 2012226 | 23-09-90 |
| | | JP-A- | 3027381 | 05-02-91 |
| | | US-A- | 5037986 | 06-08-91 |

EPO FORM P0479

For more details about this annex : see ficial Journal of the European Patent ffice, No. 12/82

International Publication No.WO 00/09506
Title of the Invention: 1H-Imidaz pyridine Derivatives
International Publication Date: February 24, 2000
International Application No.PCT/JP99/04381
Filing Date: August 12, 1999
Priority Claimed: JP10/241062 of August 12, 1998
JP11/216125 of July 30, 1999
Applicant: HOKURIKU SEIYAKU CO., LTD.
Inventors: H. KATO; J. SAKAGUCHI; M. AOYAMA; T. IZUMI; K. KATO

# DESCRIPTION

## 1H-IMIDAZOPYRIDINE DERIVATIVES

### Technical Field

The present invention relates to novel 1H-imidazopyridine derivatives and their salts, which have a powerful inhibiting effect on production of tumor necrosis factor (TNF) and interleukin-1 (IL-1) and are useful as drugs for prevention or treatment of diseases mediated by cytokines such as TNF and IL-1, including human or animal chronic inflammatory diseases (for example, rheumatoid arthritis, arthritis deformans, etc.), allergic rhinitis, atopic dermatitis, contact dermatitis, asthma, sepsis, septic shock, various autoimmune diseases [autoimmune blood diseases (for example, hemolytic anemia, hypoplastic anemia, idiopathic thrombocytopenia, etc.), autoimmune intestinal diseases (for example, ulcerative colitis, Crohn's disease, etc.), autoimmune corneitis (for example, keratoconjunctivitis sicca, vernal conjunctivitis, etc.), endocrine ophthalmopathy, Graves' disease, sarcoidosis, multiple sclerosis, systemic erythematosus, polychondritis, scleroderma, active chronic hepatitis, myasthenia gravis, psoriasis, interstitial pulmonary fibrosis, etc.], diabetes, cancer cachexia and AIDS cachexia.

### Background Art

Compounds similar to the compounds of the present invention exist, including a few compounds having a 1H-imidazoquinoline skeleton, among which are disclosed 1-(2-piperidinoethyl)-1H-

imidazo[4,5-c]quinoline in J urnal of Medical Chemistry, Vol.11, p.87 (1968), 1-isobutyl-1H-imidazo[4,5-c]quinoline-4-amine (common name: imiquimod) as a compound with antiviral action in Kokai (Japanese Unexamined Patent Publication) No. 60-123488, and 1-(2-diethylaminoethyl)-1H-imidazo[4,5-c]quinoline as a compound with analgesic/anticonvulsant action in Hungarian Patent Disclosure 34479 (Patent No. 190109); however, 1H-imidazopyridine derivatives according to the present invention have been hitherto completely unknown.

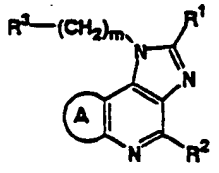
According to Journal of Interferon Research, Vol.14, p.81 (1994), the aforementioned imiquimod is known to have an inducing effect on a number of cytokines such as interferon (IFN), TNF and IL-1, but absolutely no 1H-imidazopyridine derivatives or 1H-imidazoquinoline derivatives have been hitherto known that have a production-inhibiting effect on TNF and IL-1, which is the exact opposite action from these prior art examples.

Disclosure of the Invention

It is an object of the present invention to provide novel compounds with an excellent inhibiting effect on production of cytokines such as TNF and IL-1, which are thus useful as drugs.

As a result of diligent research aimed at achieving this object, the present inventors have completed the present invention upon the discovery of novel 1H-imidazopyridine derivatives with an excellent inhibiting effect on production of TNF and IL-1.

Specifically, the invention relates to novel 1H-imidazopyridine derivatives represented by the following general formula (I):



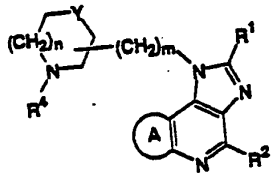

(I)

where $R^1$ represents a hydrogen atom, a hydroxyl group, an alkyl group with one or more optional substituents, a cycloalkyl group with an optional substituent, a styryl group with an optional substituent or an aryl group with one or more optional

substituents; $R^2$ represents a hydrogen atom, an alkyl group, a halogen atom, a hydroxyl group, an amino group with one or two optional substituents, a cyclic amino group with an optional substituent or a phenoxy group with an optional substituent; the A ring represents a homocyclic or heterocyclic ring optionally substituted with one or more alkyl groups, alkoxy groups or halogen atoms; $R^3$ represents a saturated nitrogen-containing heterocyclic group with an optional substituent; and m represents an integer of 0-3, with the proviso that when $R^3$ is an unsubstituted piperidino group, either or both $R^1$ and $R^2$ are not hydrogen atoms,

and to salts thereof.

According to a second mode of the invention, there are provided 1H-imidazopyridine derivatives represented by the following general formula (II):



(II)

where $R^1$, $R^2$, the A ring and m are as defined above; $R^4$ represents a hydrogen atom, an alkyl group, a benzyl group, a triphenylmethyl group, an alkanoyl group with an optional substituent, an alkoxycarbonyl group, a benzyloxycarbonyl group, a thiocarbamoyl group with an optional substituent, an alkanesulfonyl group, a benzenesulfonyl group with an optional substituent or an amidino group; Y represents a methylene group, an oxygen, sulfur or nitrogen atom, the group NH or a bond; and n represents an integer of 0-2,

and salts thereof.

According to a third mode of the invention, there are provided compounds and their salts from among compounds represented by the above general formulas (I) and (II), wherein the A ring is a benzene ring or thiophene ring.

According to another aspect there are provided drugs containing as effective ingredients any of the compounds represented by the above general formulas (I) and (II), or their

pharmacologically acceptable salts. The drugs ar useful as drugs for prevention or treatment of diseases mediat d by cytokines such as TNF and IL-1, including human and other mammalian animal chronic inflammatory diseases (for example, rheumatoid arthritis, arthritis deformans, etc.), allergic rhinitis, atopic dermatitis, contact dermatitis, asthma, sepsis, septic shock, various autoimmune diseases [autoimmune blood diseases (for example, hemolytic anemia, hypoplastic anemia, idiopathic thrombocytopenia, etc.), autoimmune intestinal diseases (for example, ulcerative colitis, Crohn's disease, etc.), autoimmune corneitis (for example, keratoconjunctivitis sicca, vernal conjunctivitis, etc.), endocrine ophthalmopathy, Graves' disease, sarcoidosis, multiple sclerosis, systemic erythematosus, polychondritis, scleroderma, active chronic hepatitis, myasthenia gravis, psoriasis, interstitial pulmonary fibrosis, etc.], diabetes, cancer cachexia and AIDS cachexia.

According to yet another aspect, there is provided the use of compounds represented by the aforementioned general formulas (I) and (II) or their pharmacologically acceptable salts for production of the aforementioned drugs, as well as a method of prevention or treatment of diseases mediated by cytokines such as TNF and IL-1, which method comprises a step of administering to a mammalian animal such as human a prophylactically or therapeutically effective dose of the compound represented by the aforementioned general formula (I) or (II) or its pharmacologically acceptable salt. The invention further provides tumor necrosis factor (TNF) production inhibitors and interleukin-1 (IL-1) production inhibitors containing as effective ingredients the compounds represented by general formulas (I) and (II) and their pharmacologically acceptable salts.

## Best Mode for Carrying Out the Invention

The compounds of general formulas (I) and (II) of the invention will be explained hereunder; the compounds represented by general formula (II) are characterized by being compounds represented by general formula (I) wherein $R^3$ is a specific saturated nitrogen-containing heterocyclic group optionally having

a specific substituent. The scope of the inv ntion is not, of course, limited to compounds represented by general formula (II), and all compounds having saturated nitrogen-containing heterocyclic groups that are optionally substituted are naturally encompassed within the scope of the invention.

As examples of alkyl groups represented by $R^1$, $R^2$ and $R^4$ in general formulas (I) and (II) there may be mentioned methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl and n-hexyl.

As examples of cycloalkyl groups represented by $R^1$ there may be mentioned cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; as examples of aryl groups represented by $R^1$ there may be mentioned phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyrazinyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 1,2,3-triazol-1-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1-tetrazolyl, 5-tetrazolyl, 1,2,5-thiadiazol-3-yl, 1-indolyl, 2-indolyl and 3-indolyl.

As examples of halogen atoms represented by $R^2$ there may be mentioned fluorine, chlorine, bromine and iodine; as examples of amino groups with one or two optional substituents represented by $R^2$ there may be mentioned amino, methylamino, ethylamino, n-propylamino, isopropylamino, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, dimethylamino, diethylamino, anilino, pyridylamino, 4-pyridylmethylamino, benzylamino, p-methoxybenzylamino and dibenzylamino; as examples of cyclic amino groups represented by $R^2$ there may be mentioned 1-aziridinyl, 1-azetidinyl, 1-pyrrolidinyl, piperidino, 1-piperazinyl, hexahydro-1H-azepin-1-yl, hexahydro-1H-1,4-diazepin-1-yl, morpholino and 4-thiomorpholinyl.

As examples of homocyclic or heterocyclic rings represented by the A ring in general formula (I) or (II) there may be



6

mentioned benzene, cyclopentene, cyclohexene, cycloheptene, cyclooctene, cycloheptadiene, thiophene, furan, pyridine, pyrazine, pyrrole, thiazole, oxazole and azepine; as examples of alkyl groups as optional substituents on these homocyclic or heterocyclic rings there may be mentioned methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl and n-hexyl; as examples of alkoxy groups as optional substituents there may be mentioned methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentyloxy, isopentyloxy, neopentyloxy and n-hexyloxy; as examples of halogen atoms as optional substituents there may be mentioned fluorine, chlorine, bromine and iodine. The number and types of such substituents are not particularly restricted, and in the case of two or more substituents they may be the same or different.

The saturated nitrogen-containing heterocyclic group represented by $R^3$ in general formula (I) represents a saturated nitrogen-containing heterocyclic group having at least one nitrogen atom as an annular atom and optionally also having oxygen or sulfur as an annular atom, and as examples there may be mentioned 1-aziridinyl, 2-aziridinyl, 1-azetidinyl, 2-azetidinyl, 3-azetidinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidino, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 2-piperazinyl, hexahydro-1H-azepin-1-yl, hexahydro-1H-azepin-2-yl, hexahydro-1H-azepin-3-yl, hexahydro-1H-azepin-4-yl, hexahydro-1H-1,4-diazepin-1-yl, hexahydro-1H-1,4-diazepin-2-yl, hexahydro-1H-1,4-diazepin-5-yl, hexahydro-1H-1,4-diazepin-6-yl, 2-morpholinyl, 3-morpholinyl, morpholino, 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl, 3-isoxazolidinyl, 3-isothiazolidinyl, 1,2,3-triazolidin-4-yl, 1,2,4-triazolidin-3-yl and 1,2,5-thiadiazolin-3-yl, among which as examples of preferred groups there may be mentioned 3-piperidyl, 4-piperidyl, 1-piperazinyl, 2-piperazinyl, 3-pyrrolidinyl, 2-azetidinyl, 3-azetidinyl, 2-morpholinyl and 2-thiomorpholinyl.

As examples of optionally substituted alkanoyl groups represented by $R^4$ in general formula (II) there may be mentioned

formyl, acetyl, propionyl, n-butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, fluoroacetyl, difluoroacetyl, trifluoroacetyl, chloroacetyl, dichloroacetyl and trichloroacetyl; as examples of alkoxycarbonyl groups represented by $R^4$ there may be mentioned methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, n-pentyloxycarbonyl and n-hexyloxycarbonyl; as examples of optionally substituted thiocarbamoyl groups represented by $R^4$ there may be mentioned thiocarbamoyl, methylthiocarbamoyl, ethylthiocarbamoyl, n-propylthiocarbamoyl, isopropylthiocarbamoyl, n-butylthiocarbamoyl, isobutylthiocarbamoyl, sec-butylthiocarbamoyl and tert-butylthiocarbamoyl; as examples of alkanesulfonyl groups represented by $R^4$ there may be mentioned methanesulfonyl, ethanesulfonyl, n-propanesulfonyl and n-butanesulfonyl.

Throughout the present specification, the substituted/bonded sites of the "aryl groups", "homocyclic or heterocyclic rings" and "saturated nitrogen-containing heterocyclic groups" will include the substitutable or bondable groups at any position so long as they are elements of the annular structure that can be substituted or bonded, unless the substituted/bonded site is particularly specified as in some of the above examples.

When a functional group "has an optional substituent" in general formula (I) or (II) of the invention it may be any group that can substitute on such a group, the number and types of substituents having no particular restrictions, and in the case of two or more substituents they may be the same or different. As examples there may be mentioned halogen atoms such as fluorine, chlorine and bromine; hydroxyl; alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl and n-hexyl; aryl groups such as trifluoromethyl, phenyl, naphthyl and pyridyl; alkoxy groups such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy; aryloxy groups such as phenoxy; optionally substituted amino groups such as amino, methylamino, ethylamino, n-propylamino, isopropylamino, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, dimethylamino,

diethylamin , anilino, pyridylamino, benzylamino, dibenzylamino, acetylamino, trifluoroacetylamino, tert-butoxycarbonylamino, benzyloxycarbonylamino, benzhydrylamino and triphenylmethylamino; alkanoyl groups such as formyl, acetyl, propionyl, n-butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, fluoroacetyl, difluoroacetyl, trifluoroacetyl, chloroacetyl, dichloroacetyl and trichloroacetyl; alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, n-pentyloxycarbonyl and n-hexyloxycarbonyl; alkylcarbamoyl groups such as benzyloxycarbonyl, carbamoyl, methylcarbamoyl, ethylcarbamoyl, n-propylcarbamoyl, isopropylcarbamoyl, n-butylcarbamoyl, isobutylcarbamoyl, sec-butylcarbamoyl and tert-butylcarbamoyl; alkylthiocarbamoyl groups such as thiocarbamoyl, methylthiocarbamoyl, ethylthiocarbamoyl, n-propylthiocarbamoyl, isopropylthiocarbamoyl, n-butylthiocarbamoyl, isobutylthiocarbamoyl, sec-butylthiocarbamoyl and tert-butylthiocarbamoyl; amidino groups; alkylthio groups such as methylthio; alkanesulfinyl groups such as methanesulfinyl; alkanesulfonyl groups such as methanesulfonyl, ethanesulfonyl, n-propanesulfonyl and n-butanesulfonyl; arylsulfonyl groups such as p-toluenesulfonyl, p-methoxybenzenesulfonyl and p-fluorobenzenesulfonyl; aralkyl groups such as benzyl, naphthyl, pyridylmethyl, furfuryl and triphenylmethyl; nitro groups; cyano groups; sulfamoyl groups; oxo groups; alkoxyimino groups such as hydroxyimino, methoxyimino, ethoxyimino, n-propoxyimino and isopropoxyimino; ethylenedioxy groups, and the like.

The compounds represented by general formulas (I) and (II) of the invention may, if desired, may be converted to salts and preferably pharmacologically acceptable salts, and they may also be dissociated from the bases of the resulting salts.

As salts, preferably pharmacologically acceptable salts, of the compounds represented by general formulas (I) and (II) of the invention there may be mentioned acid addition salts, examples of which include mineral acid salts of hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, sulfuric acid and phosphoric acid, and organic acid salts of acetic acid, propanoic acid,

butyric acid, formic acid, valeric acid, maleic acid, fumaric acid, citric acid, oxalic acid, malic acid, succinic acid, lactic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, mandelic acid, 10-camphorsulfonic acid, tartaric acid, stearic acid, gluconic acid, nicotinic acid, trifluoroacetic acid and benzoic acid.

Compounds with asymmetric carbons among the compounds represented by general formulas (I) and (II) of the invention may exist as optical isomers, and these optical isomers and their mixtures are also encompassed by the present invention.

The compounds and their salts represented by general formulas (I) and (II) of the invention may exist in any desired crystal form depending on the production conditions, or they may exist in any desired hydrated or solvated form, and these crystal forms or hydrated or solvated forms and their mixtures are also within the scope of the invention.

As examples of preferred compounds of the invention there may be mentioned the following compounds and their salts, although the invention is in no way limited to these.

(1) 4-chloro-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline

(2) 4,8-dichloro-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline

(3) 4-chloro-8-methyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline

(4) 4-chloro-8-methoxy-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline

(5) 4-chloro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline

(6) 4,8-dichloro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline

(7) 4-chloro-8-methyl-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline

(8) 4-chloro-8-methoxy-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline

(9) 4-chloro-1-[2-(4-piperidyl)ethyl]-2-trifluoromethyl-1H-imidazo[4,5-c]quinoline

(10) 4,8-dichloro-1-[2-(4-piperidyl)ethyl]-2-trifluoromethyl-1H-

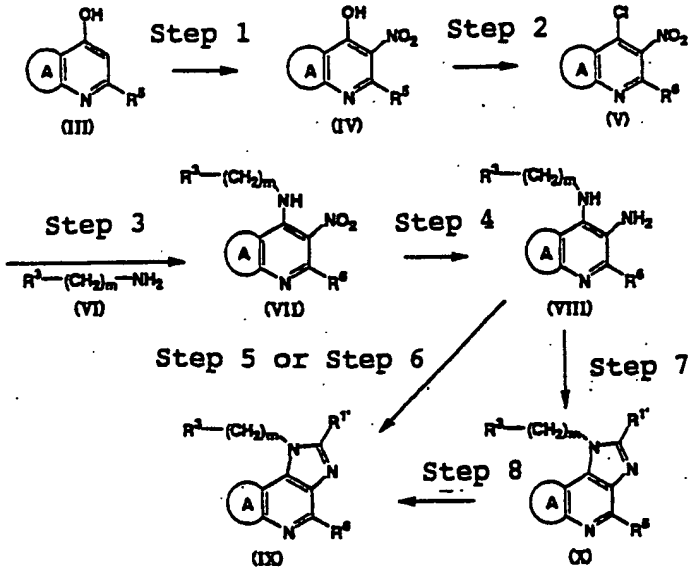
imidazo[4,5-c]quinoline
(11) 4-chloro-8-methyl-1-[2-(4-piperidyl)ethyl]-2-trifluoromethyl-1H-imidazo[4,5-c]quinoline
(12) 4-chloro-8-methoxy-1-[2-(4-piperidyl)ethyl]-2-trifluoromethyl-1H-imidazo[4,5-c]quinoline
(13) 4-chloro-2-(4-methylphenyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline
(14) 4-chloro-2-(4-methoxyphenyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline
(15) 4-chloro-2-(4-fluorophenyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline
(16) 4-chloro-1-[2-(4-piperidyl)ethyl]-2-(4-trifluoromethylphenyl)-1H-imidazo[4,5-c]quinoline
(17) 4-chloro-2-(2-furyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline
(18) 4-chloro-1-[2-(4-piperidyl)ethyl]-2-(2-thienyl)-1H-imidazo[4,5-c]quinoline
(19) 4-chloro-2-(2-imidazolyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline
(20) 4-chloro-1-[2-(4-piperidyl)ethyl]-2-(2-thiazolyl)-1H-imidazo[4,5-c]quinoline
(21) 4-chloro-2-(5-methyl-2-thienyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline
(22) 4-chloro-1-[2-(4-piperidyl)ethyl]-2-(2-pyrrolyl)-1H-imidazo[4,5-c]quinoline
(23) 4-methyl-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline
(24) 2-(4-fluorophenyl)-4-methyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline
(25) 4-methyl-1-[2-(4-piperidyl)ethyl]-2-(4-trifluoromethylphenyl)-1H-imidazo[4,5-c]quinoline
(26) 2-(2-furyl)-4-methyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline
(27) 4-methyl-1-[2-(4-piperidyl)ethyl]-2-(2-thienyl)-1H-imidazo[4,5-c]quinoline
(28) 2-(2-imidazolyl)-4-methyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline

(29) 4-methyl-1-[2-(4-piperidyl)ethyl]-2-(2-thiazolyl)-1H-imidazo[4,5-c]quinoline
(30) 4-methyl-2-(3-methyl-2-thienyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline
(31) 4-methyl-2-(5-methyl-2-thienyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline
(32) 4-methyl-1-[2-(4-piperidyl)ethyl]-2-(2-pyrrolyl)-1H-imidazo[4,5-c]quinoline
(33) 4-methyl-2-(1-methyl-2-pyrrolyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline
(34) 4-chloro-6,7,8,9-tetrahydro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline
(35) 4-chloro-6,7-dihydro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[5,4-d]cyclopenta[b]pyridine
(36) 4-chloro-2-phenyl-1-[2-(4-piperidyl)ethyl]-1H-imidazo[5,4-d]thieno[3,2-b]pyridine
(37) 4-chloro-2-phenyl-1-[2-(3-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline
(38) 4-chloro-1-[2-(2-morpholinyl)ethyl]-2-phenyl-1H-imidazo[4,5-c]quinoline
(39) 4-chloro-2-phenyl-1-[2-(1-piperazinyl)ethyl]-1H-imidazo[4,5-c]quinoline
(40) 4,6,7,8,9-pentachloro-2-ethoxymethyl-1-[2-(4-thiomorpholinyl)ethyl]-1H-imidazo[4,5-c]quinoline
(41) 4-chloro-6,7,8,9-tetrahydro-2-hydroxymethyl-1-[2-(1-piperazinyl)ethyl]-1H-imidazo[5,4-d]cyclohepta[b]pyridine
(42) 4-chloro-2-(3-methyl-2-thienyl)-1-[2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline

The novel 1H-imidazopyridine derivatives represented by general formulas (I) and (II) of the invention may be produced by various different processes, and the production processes for the invention compounds are not limited to any particular processes. The production processes described below are explained in detail for compounds represented by general formula (I), but it is self-evident that compounds represented by general formula (II) may also be produced by these production processes.

As a first synthesis process for the invention compounds, th

following synthesis process may be used as disclosed in Kokai (Japanese Unexamined Patent Publication) N . 3-206078 or in Tetrahedron, Vol.51, p.5813 (1995).




where $R^5$ represents hydroxyl or an alkyl group; $R^6$ represents chlorine or an alkyl group; $R^{1'}$ has the same definition as $R^1$ above (but is not hydroxyl), and $R^3$, m and the A ring are as defined above.

Specifically, in step 1, a compound represented by general formula (III) may be reacted with a nitrating agent such as concentrated nitric acid or fuming nitric acid in the presence or in the absence of acetic acid, sulfuric acid or the like, at a temperature between 0°C and 200°C, to obtain a compound of general formula (IV).

In step 2, the compound of general formula (IV) may be reacted with an appropriate chlorinating agent, such as phosphorus oxychloride, thionyl chloride, phosgene, oxalyl chloride or phosphorus pentachloride in the presence or in the absence of a solvent such as toluene, at a temperature between 0°C and 200°C, to obtain a compound of general formula (V).

In step 3, the compound of general formula (V) may be reacted with an amine represented by general formula (VI) in a solvent such as N,N-dimethylformamide or toluene in the presence or in the absence f a base such as triethylamine or potassium carbonate, at

a temperature from -10°C to the reflux temperature of the solvent, to obtain a compound of general formula (VII).

In step 4, the nitro group of the compound of general formula (VII) may be reduced by an appropriate reduction method, for example, catalytic reduction using a metal catalyst such as platinum, Raney nickel or palladium carbon, a reduction method using nickel chloride or sodium borohydride, or a reduction method using iron powder and hydrochloric acid, to obtain a compound of general formula (VIII).

The reduction reaction may be carried out in a solvent such as water, methanol, ethanol, tetrahydrofuran or a mixed solvent thereof, at a temperature from 0°C to the reflux temperature of the solvent.

In step 5, the compound of general formula (VIII) may be reacted with a compound represented by one of the following general formulas (XI), (XII) or (XIII):

$R^{1'}C(OR)_3$ (XI)

$R^{1'}COX$ (XII)

$(R^{1'}CO)_2O$ (XIII)

where R represents a lower alkyl group, X represents a halogen atom and $R^{1'}$ has the same definition as $R^1$ above (but is not hydroxyl),
in the presence or in the absence of a basic catalyst such as triethylamine or an acid catalyst such as hydrochloric acid or p-toluenesulfonic acid, and in the presence or in the absence of a solvent such as N,N-dimethylformamide, tetrahydrofuran, acetonitrile, xylene or toluene, at a temperature from 0°C to 200°C, to obtain a compound of general formula (IX).

As an alternative to step 5, in step 6 the compound of general formula (VIII) may be reacted with a compound represented by the following general formula (XIV):

$R^{1'}CHO$ (XIV)

where $R^{1'}$ has the same definition as $R^1$ above (but is not hydroxyl), in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in a solvent such as acetonitrile, 1,4-dioxane or tetrahydrofuran, at a temperature from 0°C to the reflux temperature of the solvent, to obtain a compound of general formula (IX).

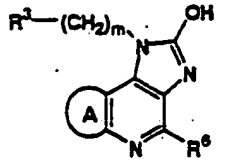
As a further alternative t step 5 or step 6, in step 7 the compound of general formula (VIII) may be reacted with a c mpound represented by the following general formula (XV):

$$R^{1'}COOH \qquad (XV)$$

where $R^{1'}$ has the same definition as $R^1$ above (but is not hydroxyl), in the presence or in the absence of an acid catalyst such as hydrochloric acid or sulfuric acid, and in the presence or in the absence of a solvent such as N,N-dimethylformamide or toluene, at a temperature from 0°C to 200°C, to obtain a compound of general formula (X); when $R^5$ in general formula (X) is hydroxyl, the compound of general formula (IX) may be obtained by chlorination in step 8.

The chlorination reaction may be carried out by first, if necessary, protecting the compound of general formula (X) at the nitrogen atoms not bonded to the $(CH_2)_m$ group adjacent to the saturated nitrogen-containing heterocyclic group represented by $R^3$ by a common method with a protecting group such as an alkanoyl group, and then using an appropriate chlorinating agent, such as phosphorus oxychloride, thionyl chloride, phosgene, oxalyl chloride or phosphorus pentachloride for reaction in the presence or in the absence of a solvent such as toluene, at a temperature between 0°C and 200°C, and subsequently deprotecting by a common method if necessary, to obtain a compound of general formula (IX) wherein $R^6$ is a chlorine atom.

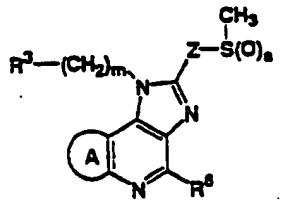
As a second synthesis process for the invention compounds, the compound of general formula (VIII) may be reacted with triphosgene in the presence of a base such as triethylamine or potassium carbonate, in a solvent such as 1,2-dichloroethane, 1,4-dioxane, tetrahydrofuran, N,N-dimethylformamide or toluene, at a temperature from 0°C to the reflux temperature of the solvent, to obtain a compound of general formula (XVI).




(XVI)

where $R^3$, $R^6$, m and the A ring are as defined above.

As a third synthesis process for the invention compounds, a compound of general formula (IX) having a methylthio-substituted aryl group as the $R^{1'}$ substituent may be subjected t an appropriate oxidation reaction, if necessary after protecting the nitrogen atoms not bonded to the $(CH_2)_m$ group adjacent to the saturated nitrogen-containing heterocyclic group represented by $R^3$ by a common method with a protecting group such as an alkanoyl group, in which case it is subsequently deprotected by a common method, to obtain a compound represented by general formula (XVII)



(XVII)

where Z represents an aromatic ring, a represents an integer of 1 or 2, and $R^3$, $R^6$, m and the A ring are as defined above.

The oxidation reaction may be carried out by any of various methods, depending on the target compound. Specifically, when a is an integer of 1, an oxidizing agent such as chromic acid, hydrogen peroxide, m-chloroperoxybenzoic acid, sodium periodate or potassium periodate may be used, and when a is an integer of 2, an oxidizing agent such as chromic acid, hydrogen peroxide, m-chloroperoxybenzoic acid, osmium tetraoxide or ruthenium tetraoxide may be used, for reaction in tetrahydrofuran, 1,4-dioxane, 1,2-dichloroethane, methanol, acetone or water, or a mixed solvent thereof, at a temperature from 0°C to the reflux temperature of the solvent.

As a fourth synthesis process for the invention compounds, a compound of general formula (I) wherein $R^2$ is a chlorine atom may be reacted using water or an appropriate acid or base in a solvent at a temperature from 0°C to the reflux temperature of the solvent, to obtain a compound of general formula (I) wherein $R^2$ is hydroxyl. As examples of appropriate acids there may be mentioned organic acids such as formic acid, acetic acid or trifluoroacetic acid and mineral acids such as hydrochloric acid, sulfuric acid and hydrobromic acid; as examples of appropriate bases there may be

mentioned hydroxides, carbonates and bicarbonates of alkali metals such as sodium and potassium or alkaline earth metals such as magnesium and calcium; and as examples of solvents there may be mentioned alcohols such as methanol, ethanol and n-propanol, solvents such as N,N-dimethylformamide, 1,4-dioxane and tetrahydrofuran, or aqueous solvents containing them.

As a fifth synthesis process for the invention compounds, a compound obtained by reacting a compound of general formula (I) wherein $R^2$ is a chlorine atom and $R^1$ is $R^{1'}$, or a compound of general formula (I) wherein $R^2$ is hydroxyl and $R^1$ is $R^{1'}$ with trifluoromethanesulfonic anhydride, methanesulfonyl chloride or p-toluenesulfonyl chloride, may be reacted with a metal halide (for example, potassium fluoride, sodium fluoride, lithium fluoride, potassium bromide, sodium bromide, potassium iodide or sodium iodide) in a polar aprotic solvent such as dimethylsulfoxide, N,N-dimethylformamide or acetonitrile, in the presence or in the absence of a phase-transfer catalyst such as tetraphenylphosphonium bromide, hexadecyltributylphosphonium bromide or 18-crown-6 and at a temperature from 0°C to the reflux temperature of the solvent, to obtain a compound of general formula (I) wherein $R^2$ is a fluorine atom, bromine atom or iodine atom and $R^1$ is $R^{1'}$.

As a sixth synthesis process for the invention compounds, a compound of general formula (I) wherein $R^3$ is a saturated nitrogen-containing heterocyclic group having a protecting group such as an alkanoyl, alkoxycarbonyl, benzyl or trifluoromethyl group on a nitrogen atom not bonded to the adjacent $(CH_2)_m$ group, is subjected to deprotecting reaction using an acid or alkali or to catalytic reduction reaction using a metal catalyst, depending on the type of protecting groups on the nitrogen atoms, to obtain a compound of general formula (I) wherein $R^3$ is a saturated nitrogen-containing heterocyclic group which is deprotected at a nitrogen atom not bonded to the adjacent $(CH_2)_m$ group.

The deprotecting reaction using an acid or alkali may be carried out by using an appropriate acid or base for reaction in a solvent in the presence or in the absence of a cation scavenger such as anisole or thioanisole. As examples of solvents to be

used there may be mentioned ethyl acetate, methylene chloride, 1,2-dichloroethane, 1,4-dioxane, methanol, ethanol, n-propanol, N,N-dimethylformamide, tetrahydrofuran, water or mixed solvents thereof; as examples of acids to be used there may be mentioned hydrochloric acid, hydrogen chloride/ethyl acetate solution, hydrogen chloride/ethanol solution, sulfuric acid, hydrobromic acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid, formic acid and acetic acid; and as examples of bases to be used there may be mentioned hydroxides, carbonates and bicarbonates of alkali metals such as sodium and potassium or alkaline earth metals such as magnesium and calcium; the reaction may be conducted at a temperature from 0°C to the reflux temperature of the solvent.

The catalytic reduction reaction may be carried out using an appropriate metal catalyst such as platinum, palladium carbon, Raney nickel or Perlman's reagent, in water, an alcohol such as methanol, ethanol or n-propanol, acetic acid, or a mixed solvent thereof, in the presence or in the absence of an acid such as hydrochloric acid, at from room temperature to the reflux temperature of the solvent and under a pressure of from ordinary pressure to 200 $kg/cm^2$.

As a seventh synthesis process for the invention compounds, a compound of general formula (I) wherein $R^2$ is a chlorine atom may be reacted with an optionally substituted phenol derivative in the presence of a base such as sodium hydroxide or potassium hydroxide, and in the presence or in the absence of a solvent such as N,N-dimethylformamide or toluene, at a temperature from 0°C to 200°C, to obtain a compound of general formula (I) wherein $R^2$ is an optionally substituted phenoxy group.

As an eighth synthesis process for the invention compounds, a compound of general formula (I) wherein $R^2$ is an optionally substituted phenoxy group obtained by the seventh synthesis process may be reacted with ammonium acetate in the presence or in the absence of a solvent such as N,N-dimethylformamide or toluene, at a temperature from 0°C to 200°C, to obtain a compound of general formula (I) wherein $R^2$ is an amino group.

As a ninth synthesis process for the invention compounds, a

compound of general formula (I) wherein $R^2$ is a chlorine atom may be reacted with an amine derivative having one or two optional substituents or a cyclic amine derivative having an optional substituent, in the presence or in the absence of a base such as triethylamine, potassium carbonate or sodium hydroxide and in the presence or in the absence of a solvent such as water, an alcohol such as methanol, ethanol or n-propanol, methylene chloride, 1,2-dichloroethane, N,N-dimethylformamide, 1,4-dioxane, tetrahydrofuran or toluene, at a temperature from 0°C to 200°C and under ordinary pressure or under pressurization, to obtain a compound of general formula (I) wherein $R^2$ is an amino group with one or two optional substituents or a cyclic amino group with an optional substituent.

As a tenth synthesis process for the invention compounds, a compound of general formula (I) wherein $R^2$ is a benzylamino, dibenzylamino or p-methoxybenzylamino group, obtained by the ninth synthesis process, is subjected to catalytic reduction using an appropriate metal catalyst, or a compound wherein $R^2$ is p-methoxybenzylamino is subjected to deprotecting reaction using an acid, to obtain a compound of general formula (I) wherein $R^2$ is an amino group.

The catalytic reduction reaction may be carried out at ordinary pressure or under pressurization, in an alcohol such as methanol or ethanol, in water, or in a mixed solvent thereof, at a temperature from room temperature to the reflux temperature of the solvent, in the presence or in the absence of an acid such as hydrochloric acid, acetic acid or formic acid, or ammonium formate, cyclohexene, cyclohexadiene or the like, using a metal catalyst such as palladium carbon of Perlman's reagent, at ordinary pressure or under a pressure of 200 $kg/cm^2$. The deprotecting reaction using an acid may be carried out in a solvent, for example, an alcohol such as methanol or ethanol, methylene chloride, 1,2-dichloroethane, 1,4-dioxane, tetrahydrofuran, toluene or N,N-dimethylformamide, in the presence or in the absence of a cation scavenger such as anisole or thioanisole, using an acid such as hydrochloric acid, sulfuric acid, trifluor acetic acid or trifluoromethanesulfonic acid, at a

temperature from 0°C t the reflux temperature of the solvent.

As a eleventh synthesis process for the invention compounds, a compound of general formula (I) wherein $R^3$ is a saturated nitr gen-containing heterocyclic group having an ethylenedioxy group as a substituent, is reacted using an acid such as hydrochloric acid, hydrogen chloride/ethyl acetate solution, hydrogen chloride/ethanol solution, sulfuric acid, hydrobromic acid, trifluoroacetic acid, p-toluenesulfonic acid, formic acid or acetic acid, in the presence or in the absence of a solvent such as ethyl acetate, methylene chloride, 1,4-dioxane, tetrahydrofuran, methanol, ethanol, n-propanol or N,N-dimethylformamide, or an aqueous solvent thereof, at a temperature from 0°C to 200°C, to obtain a compound of general formula (I) wherein $R^3$ is a saturated nitrogen-containing heterocyclic group having an oxo group as a substituent.

As a twelfth synthesis process for the invention compounds, a compound of general formula (I) wherein $R^3$ is a saturated nitrogen-containing heterocyclic group having an oxo group as a substituent, obtained by the eleventh synthesis process, may be reacted with a compound represented by the following general formula (XVIII):

$$R^7\text{-}O\text{-}NH_2 \qquad \text{(XVIII)}$$

where $R^7$ represents hydrogen or an alkyl group,
in the presence or in the absence of a base such as triethylamine, diisopropylethylamine, sodium carbonate, potassium carbonate, sodium bicarbonate or sodium acetate, in a solvent which is an alcohol such as methanol, ethanol or n-propanol or N-N-dimethylformamide, 1,4-dioxane, tetrahydrofuran or toluene, at a temperature from 0°C to the reflux temperature of the solvent, to obtain a compound of general formula (I) wherein $R^3$ is a saturated nitrogen-containing heterocyclic group having a hydroxyimino or alkoxyimino group as a substituent.

As a thirteenth synthesis process for the invention compounds, a compound of general formula (I) wherein $R^2$ is a chlorine atom may be subjected to catalytic reduction with a metal catalyst such as platinum or palladium carbon in the presence or in the absence of an acid such as hydrochloric acid or acetic acid, in an alcohol solvent such as methanol or ethanol or an aqueous solvent thereof,

under ordinary pressure and at a temperature from room temperature to the reflux temperature of the solvent, t obtain a comp und of general formula (I) wherein $R^2$ is hydrogen.

As a fourteenth synthesis process for the invention compounds, a compound of general formula (I) wherein $R^3$ is a saturated nitrogen-containing heterocyclic group having no protecting groups on nitrogen atoms not bonded to the adjacent $(CH_2)_m$ group, may be reacted using an appropriate reagent to obtain a compound of general formula (I) wherein $R^3$ is a saturated nitrogen-containing heterocyclic group having an appropriate substituent on a nitrogen atom not bonded to the adjacent $(CH_2)_m$ group.

The reaction may be carried out in the presence or in the absence of a solvent such as N,N-dimethylformamide, methylene chloride, tetrahydrofuran, toluene, pyridine, nitrobenzene, 1,2-dichloroethane, 1,4-dioxane, methanol, ethanol, n-propanol, water, or a mixed solvent thereof, and in the presence or in the absence of a base such as triethylamine or potassium carbonate, at a temperature from 0°C to 200°C.

As examples of appropriate reagents there may be mentioned alkyl halides, triphenylmethyl chloride, benzyl chloride, benzhydryl chloride, formic acid/formalin mixture, acetyl chloride, acetic anhydride, trifluoroacetic anhydride, benzoyl chloride, benzyl chlorocarbonate, ethyl chlorocarbonate, di-tert-butyl dicarbonate, sodium cyanate, alkyl isocyanate, sodium thiocyanate, alkyl isothiocyanate, 1H-pyrazole-1-carboxamidine, methanesulfonyl chloride, p-toluenesulfonyl chloride, p-fluorobenzenesulfonyl chloride, urethane, alkylurethane, thiourethane and alkylthiourethane.

As a fifteenth synthesis process for the invention compounds, a compound of general formula (I) wherein $R^3$ is a saturated nitrogen-containing heterocyclic group having an alkyl group or benzyl group as a substituent on a nitrogen atom not bonded to the adjacent $(CH_2)_m$ group, may be reacted with alkyl chlorocarbonate or benzyl chlorocarbonate in the presence or in the absence of a solvent such as methylene chloride or toluene, and in the presence or in the absence of a base such as triethylamine or potassium carbonate, at a temperature from 0°C t 200°C, t obtain a

compound of general formula (I) wherein $R^3$ is a saturated nitrogen-c ntaining heterocyclic group having an alkoxycarbonyl group or benzyloxycarbonyl group as a substituent on a nitrogen atom not bonded to the adjacent $(CH_2)_m$ group.

Some of the compounds represented by general formulas (III) to (VIII) that serve as starting materials or intermediates in the production processes for the invention compounds are publicly known compounds, and are disclosed for example in Journal of Medicinal Chemistry, Vol.18, p.726 (1975), Vol.33, p.1880 (1990) and Vol.40, p.1779 (1997), in International Patent Publication No. WO97/20820 and in European Patent Publication No. 223124 (1987), and may be produced by the processes described therein. Production processes for some novel compounds are also described as reference examples.

Drugs containing as effective ingredients the novel 1H-imidazopyridine derivatives represented by the aforementioned general formulas (I) and (II) that are produced in this manner, or their salts, are usually administered as oral preparations such as capsules, tablets, fine particles, granules, powders, syrups, dry syrups or the like, or as parenteral preparations such as injections, suppositories, eyedrops, ophthalmic ointments, eardrops, dermatological agents, inhalants or the like. These preparations may be produced by a common method with inclusion of pharmacologically and pharmaceutically acceptable additives. For example, in the case of oral preparations and suppositories there may be used such formulating components such as excipients (lactose, D-mannitol, corn starch, crystal cellulose, etc.), disintegrating agents (carboxymethylcellulose, carboxymethylcellulose calcium, etc.), binders (hydroxypropylcellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, etc.), lubricants (magnesium stearate, talc, etc.), coating agents (hydroxypropylmethyl cellulose, saccharose, titanium oxide, etc.), bases (polyethylene glycol, hard fat, etc.); in the case of injections, eyedrops and eardrops there may be used such formulating components as dissolving agents or dissolving aids that are either aqueous or can form solutions at the time of use (distilled water for injection, physiological

saline, propylene glycol, etc.), pH adjustors (inorganic or organic acids or bases), isotonizing agents (salt, gluc se, glycerin, etc.), stabilizers and the like; and in the case of ophthalmic ointments and dermatological agents there may be used such appropriate formulating components as ointments, creams and skin patches (white vaseline, macrogol, glycerin, cotton cloth, etc.).

The dosage of any of the compounds for a patient being treated will differ on the symptoms of the patient, but for healthy adults the daily administration dosage may be about 0.1-1000 mg for oral administration and about 0.01-500 mg for parenteral administration per day, either once or in divided doses. The dosage is, of course, preferably adjusted as appropriate depending on the purpose of treatment or prevention, the site and nature of the disease and the age and symptoms of the patient.

——— (Examples not translated) ———

The following are test results for the inhibiting effect on TNF-$\alpha$ production and the inhibiting effect on IL-1ß production in human cells, as demonstrations of the excellent effect of the compounds of the invention.

1. Preparation of blood cells for culturing

Whole blood in an amount of about 50 ml was taken by intravenous penetration from a healthy adult volunteer into a plastic test tube containing 170 $\mu$l of Novo Heparin Injection 1000 (Novo Nordisk A/S). Peripheral Blood Mononuclear Cells (PBMC) were prepared from this blood with a LeucoPREP™ (Becton Dickinson) cell separation tube, and the cells were cultured to a cell density of 1 x $10^6$ cells/ml in RPMI-1640 medium (Nissui Seiyaku, KK.) containing 2 mM L-glutamine (Life Technologies) and 2.5 U/ml penicillin-2.5 $\mu$g/ml streptomycin solution (Life Technologies), with addition of 10% fetal calf serum (Intergen Company).

2. Preparation of test compound

The test compound of interest was dissolved in sterilized ultrapurified water, dimethylsulfoxide or 0.1 N hydr chloric acid

to a concentration of 20 μM, and used after serial dilution with physiological saline. The compound was tested in a concentration range of $10^{-10}$ M to $10^{-5}$ M.

3. Drug treatment of cells

After adding 180 μl of PBMC in the aforementioned medium into a 96-well (flat-bottom) MicroTest III™ tissue culture plate (Becton Dickinson), 10 μl of 1 μg/ml lipopolysaccharide (LPS) was added. After 30 minutes, 10 μl of the test compound solution or solvent was added into each well, the plate was covered with a plastic lid, and the cells were incubated at 37°C for 16 hours in a 5% carbon dioxide atmosphere.

4. Quantitation of human TNF-α and human IL-1β

An enzyme immunoassay system was constructed according to the sandwich method to quantify the human TNF-α and human IL-1β in the culture supernatants. Diluted anti-cytokine antibody (primary antibody) was introduced into the 96-well microtiter plate as a coating. After washing the wells, the culture supernatants were appropriately diluted and placed in the wells for incubation. Next, secondary antibody for the cytokines and tertiary antibody for the secondary antibody were introduced in that order, with a washing step between each introduction. After the final washing, tetramethylbenzine solution (DAKO) was introduced into each well to initiate a coloring reaction. After suspending the coloring reaction with 1 N sulfuric acid, the absorption of each well at 450 nm was measured with an M-Vmax™ microplate reader (Molecular Devices). The cytokine concentration was determined by comparison with a calibration curve for standard recombinant cytokine using the quantitation software Softmax™ (Molecular Devices). The human TNF-α was quantified using monoclonal anti-human TNF-α (ENDOGEN), polyclonal rabbit anti-human TNF-α (Pharma Biotechnologie Hannover), peroxidase-conjugated donkey anti-rabbit IgG (Jackson Immuno Res. Labs.) and recombinant human TNF-α (INTERGEN) as the primary, secondary and tertiary antibody and the calibration curve standard, respectively. The human IL-1β was quantified using mon clonal anti-human IL-1β (Cistron), polyclonal sheep anti-human IL-1β (Biogenesis), HRP-conjugated donkey anti-goat IgG (Chemicon

International) and recombinant human IL-1ß (R&D Systems) as the primary, secondary and tertiary antibody and the calibration curve standard, respectively.

The activity of each test compound for both the TNF-α and IL-1ß was expressed as a percent (%) of the cytokine induction upon treatment with LPS and the test compound, divided by the cytokine induction upon treatment with LPS alone.

The results are shown in Tables 1 and 2.

Table 1 Inhibiting effect on TNF-α production in human cells

| Compound | Dose concentration (μmol) | | | | |
|---|---|---|---|---|---|
| | 0.001 | 0.01 | 0.10 | 1.0 | 10 |
| Example 89 | 91 | 86 | 90 | 84 | 17 |
| Example 110 | 80 | 77 | 26 | 1 | 0 |
| Example 113 | 68 | 81 | 86 | 69 | 29 |
| Example 117 | 117 | 77 | 71 | 24 | 0 |
| Example 118 | 79 | 91 | 88 | 51 | 3 |
| Example 121 | 81 | 91 | 49 | 0 | 0 |

Table 2 Inhibiting effect on IL-1ß production in human cells

| Chemical compound | Dose concentration (μmol) | | | | |
|---|---|---|---|---|---|
| | 0.001 | 0.01 | 0.10 | 1.0 | 10 |
| Example 89 | 112 | 102 | 96 | 63 | 0 |
| Example 110 | 119 | 105 | 85 | 64 | 14 |
| Example 113 | 104 | 109 | 116 | 96 | 30 |
| Example 117 | 119 | 106 | 111 | 72 | 8 |
| Example 118 | 96 | 106 | 102 | 59 | 0 |
| Example 121 | 102 | 108 | 87 | 24 | 0 |

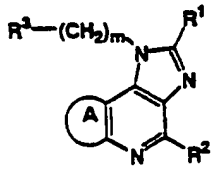
These results demonstrate that the compounds of the invention exhibit an excellent inhibiting effect on production of TNF and IL-1.

Industrial Applicability

The compounds of the invention exhibit an excellent inhibiting effect on production of TNF and IL-1, and are therefore highly useful for the prevention or treatment of diseases attributed to these cytokines.

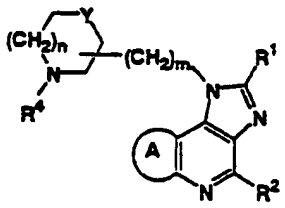
## CLAIMS

1. A 1H-imidazopyridine derivative represented by the following general formula:



where $R^1$ represents a hydrogen atom, a hydroxyl group, an alkyl group with one or more optional substituents, a cycloalkyl group with an optional substituent, a styryl group with an optional substituent or an aryl group with one or more optional substituents; $R^2$ represents a hydrogen atom, an alkyl group, a halogen atom, a hydroxyl group, an amino group with one or two optional substituents, a cyclic amino group with an optional substituent or a phenoxy group with an optional substituent; the A ring represents a homocyclic or heterocyclic ring optionally substituted with one or more alkyl groups, alkoxy groups or halogen atoms; $R^3$ represents a saturated nitrogen-containing heterocyclic group with an optional substituent; and m represents an integer of 0-3, with the proviso that when $R^3$ is an unsubstituted piperidino group, either or both $R^1$ and $R^2$ are not hydrogen atoms,
or a salt thereof.

2. A 1H-imidazopyridine derivative represented by the following general formula:



where $R^1$ represents a hydrogen atom, a hydroxyl group, an alkyl group with one or more optional substituents, a cycloalkyl group with an optional substituent, a styryl group with an optional substituent or an aryl group with one or more optional substituents; $R^2$ represents a hydrogen atom, an alkyl group, a halogen atom, a hydroxyl group, an amino group with one or two optional substituents, a cyclic amino group with an optional

substituent or a phenoxy gr up with an optional substituent; the A ring represents a homocyclic or heterocyclic ring optionally substituted with one or more alkyl groups, alk xy groups or halogen atoms; m represents an integer of 0-3; $R^4$ represents a hydrogen atom, an alkyl group, a benzyl group, a triphenylmethyl group, an alkanoyl group with an optional substituent, an alkoxycarbonyl group, a benzyloxycarbonyl group, a thiocarbamoyl group with an optional substituent, an alkanesulfonyl group, a benzenesulfonyl group with an optional substituent or an amidino group; Y represents a methylene group, an oxygen, sulfur or nitrogen atom, the group NH or a bond; and n represents an integer of 0-2,
or a salt thereof.

3. A compound or its salt according to claim 1 or 2, wherein the A ring is a benzene ring or thiophene ring.

4. A drug containing as an effective ingredient a 1H-imidazopyridine derivative according to claim 1 or 2, or a pharmacologically acceptable salt thereof.

5. A drug according to claim 4, which is used for prevention or treatment of cytokine-mediated diseases.